Mechanisms of clonal evolution in childhood acute lymphoblastic leukemia.

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Public Summary:
Childhood acute lymphoblastic leukemia (ALL) can often be traced to a pre-leukemic clone carrying a prenatal genetic lesion. Postnatally acquired mutations then drive clonal evolution toward overt leukemia. The enzymes RAG1-RAG2 and AID, which diversify immunoglobulin-encoding genes, are strictly segregated in developing cells during B lymphopoiesis and peripheral mature B cells, respectively. Here we identified small pre-BII cells as a natural subset with increased genetic vulnerability owing to concurrent activation of these enzymes. Consistent with epidemiological findings on childhood ALL etiology, susceptibility to genetic lesions during B lymphopoiesis at the transition from the large pre-BII cell stage to the small pre-BII cell stage was exacerbated by abnormal cytokine signaling and repetitive inflammatory stimuli. We demonstrated that AID and RAG1-RAG2 drove leukemic clonal evolution with repeated exposure to inflammatory stimuli, paralleling chronic infections in childhood.

Scientific Abstract:
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